SCIENTIFIC ABSTRACT

Patients baring tumors of different histologic origin have elevated levels of Transforming Growth Factors-βs (TGF-βs), which are associated with immunosuppression. TGF-βs suppress T-cells activation in part by inhibiting the gamma chain of high affinity cytokine receptor.

Genetic modification of tumor cells to block their of TGF-β secretion has made the tumor cells more immunogenic and suitable for active immunotherapy. We have shown the efficacy of this approach in four different tumor models, a murine squamous NSCLC (KLN-205), two rat glial tumors, and one murine ovarian teratoma (MOT). Others have also shown the efficacy of TGF-β gene therapy in inducing anti tumor effects in cultured cells and animal tumor models.

In the murine lung carcinoma two injections with 5 x 10^5 TGF-β2 antisense gene modified cells protected the animals against a subsequent intra peritoneal tumor challenge with 10^6 cells. In the rat 9L glial tumor model inoculation of tumor bearing rats with TGF-β antisense gene modified 9L cells resulted in eradication of intracranial tumors in all animals. In the second glial tumor, the low TGF-β producing C-6 glioma, TGF-β antisense gene therapy eradicated intracranial tumors in 60 percent of animals. In the murine ovarian teratoma (MOT) tumor model, however, only the group inoculated with TGF-β antisense and IL-2 gene modified cells resulted in protection of approximately 70% of animals from a subsequent tumor challenge. This protection level was significantly higher than protection in the control groups treated with all other combinations. *In vitro* cytotoxicity assays in animal tumor models using lymph node effector cells taken from immunized animals and activated *in vitro* in the presence of irradiated tumor cells and 50 BRMP units of IL-2 revealed a 4-to-8 fold increase in lytic activity for the animals immunized with TGF-β2 antisense gene modified tumor cells compare to control groups.

Following FDA approval, we have tested this approach in a phase I clinical trial in patients with glioblastoma. In this study we have thus far shown that injections of either 5 x 10^6, 1 x 10^7, or 2 x 10^7 TGF-β antisense gene modified autologous tumor cells is safe and does not cause toxicity. Immune histology of injection site biopsies and secondary tumor resections demonstrated significantly higher number of immune infiltrates in comparison to biopsies taken prior to initiation of gene therapy.

Based on the data presented above, we propose to treat non-small cell lung cancer patients in a phase II clinical trial that consists of three separate cohorts. The vaccine cocktail will consist of equal number of each of the four irradiated TGF-β antisense gene modified NSCLC cell lines. The number of injected cells in the three cohorts will be 1.25 x 10^7, 2.5 x 10^7, and 5 x 10^7 cells respectively.

Patients will be monitored and evaluated according to standard evaluation criteria of no response, stable disease, partial response and complete response. The results of this study will be used to evaluate the feasibility of a phase III clinical trial with TGF-β antisense gene modified tumor cells alone and in combination with other cytokines.